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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application

New York, New York

Masaji ISHIGURO, et al.

April 3, 2000

Serial No.: 09/178,594

Group Art Unit: 1611

Filed: October 26, 1998

Examiner: Mark L. Berch

For: PROCESS FOR SYNTHESIZING 4-SUBSTITUTED AZETIDINONE  
DERIVATIVES

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Hon. Commissioner of Patents and Trademarks

Washington D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the Final Rejection of claims 15-19,  
the only claims remaining in the application.

(1) Real Party in Interest

Suntory Limited of Osaka, Japan is the Assignee of the above-  
identified application by virtue of an Assignment dated August 30,  
and September 2, 6 and 7 and recorded on October 11, 1994 at Reel  
7224, Frame 0706.

(2) Related Appeals and Interferences

There are no related Appeals or Interferences regarding the  
above-identified application.

(3) Status of Claims

Claims 15-19 are the only claims remaining in this application. No claim has been allowed. Accordingly, this Appeal is directed to claims 15-19.

(4) Status of Amendments

With their response dated July 12, 1999, applicants amended claim 15 to more clearly define their invention. Minor changes were also made to claims 16 and 18.

Applicants did not file a response to the Final Rejection of August 6, 1999.

Applicants have filed concurrently with this Appeal Brief an amendment requesting correction of some minor errors and some misspellings in claim 15 which are of a formal nature. In the event that this amendment is entered, a Substitute Appendix of the claims is enclosed wherein claim 15 includes the requested changes.

(5) Summary of the Invention

The invention as set forth in claims 15, and 16-19 which are dependent on claim 15, is directed to a process for synthesizing 4-substituted azetidinones by the reactions of an azetidinone derivative in the presence of a copper or copper-zinc catalyst.

The invention provides a streamlined process for the preparation of 4-substituted azetidinone derivatives which

essentially comprises replacement of  $-SR_2$  with  $-C(X)(Y)CO_2R_3$  in the presence of a copper compound or a mixture of zinc with a copper compound.

(6) Issue

Whether claims 15-19 describe applicants' invention in such full, clear and expert terms as to enable any person skilled in the art to make and use the same, and/or whether such claims fail to particularly point out and distinctly claim the subject matter which applicants regard as their invention.

(7) Grouping of Claims

All of claims 15-19 are directed to the same invention and preferred embodiments thereof.

(8) Arguments

Applicants respectfully submit that claims 15-19 are in compliance with the requirements of 35 USC 112, first and second paragraphs.

Applicants respectfully submit that the language used in claim 15 to describe the  $R_3$  group is proper. It should be noted that applicants claims are not directed to compositions of matter, but to a process for the preparation of certain azetidinone derivatives. The reaction essentially comprises the replacement of  $-SR_2$  with  $-C(X)(Y)CO_2R_3$  in which the R groups are not involved in the substitution reactions. Hence, one of ordinary skill in

the art to which this invention pertains, would be aware that a wide selection of R groups could be employed as long as they do not adversely affect the substitution reactions.

On page 13, line 13 et seq., applicants have indicated that the  $R_3$  group is not particularly limited. The only requirement is that it can be eliminated from the esterified carboxyl group represented by  $CO_2R_3$  through hydrolysis. A wide variety of esters are set forth at lines 19, et seq. Applicants submit that in the absence of prior art and in view of the large number of ester groups described, it would be unduly limiting to be required to restrict the  $R_3$  group, particularly since it does not undergo any change in the substitution reaction.

The Examiner had questioned in the Office Action of January 12, 1999 in paragraph number 3, the source of certain groups which define the X and Y groups. It should be noted that on page 2, lines 13 et seq. of the specification, that such groups include substituted or unsubstituted ester groups and substituted or unsubstituted thioester groups.

In their specification on pages 1 and 2, applicants have defined the X and Y groups of formula [3] and have indicated that such groups can be further substituted. On pages 15 et seq., numerous preferred examples of the groups represented by X and Y are set forth. On page 17 of applicants' specification at lines 3

et seq., a wide variety of substituents are cited which can be present. While it may not be possible that each and every combination of X and/or Y with the substituent disclosed may exist chemically, it is respectfully submitted that this should not be a bar to applicants defining X, Y and possible substituents in their claims.

With respect to the  $R_1$ ,  $R_2$ ,  $R_3$  and X and Y groups and the numerous examples given in the applicants specification, one of ordinary skill would be aware that a wide variety of organic radicals could be present as long as they do not adversely affect the substitution reactions. In the working examples, the substituent groups represent several diverse groups. For instance, in Examples:  $R_1 = t\text{-Bu}(\text{Me})_2\text{Si-}$ ,  $R_2 = \text{Phenyl}$ ,  $R_3 = \text{Me}$ , and X and Y = H and COOMe in Example 1;  $R_1 = t\text{-Bu}(\text{Me})_2\text{Si-}$ ,  $R_2 = \text{Phenyl}$ ,  $R_3 = \text{Et}$ , and X and Y = Me and -COOEt in Example 2;  $R_1 = t\text{-Bu}(\text{Me})_2\text{Si-}$ ,  $R_2 = \text{Phenyl}$ ,  $R_3 = \text{Et}$ , and X and Y = F and -COOEt in Example 3;  $R_1 = t\text{-Bu}(\text{Me})_2\text{Si-}$ ,  $R_2 = \text{Phenyl}$ ,  $R_3 = \text{Et}$ , and X and Y = Me and (Me)-CO in Example 5;  $R_1 = t\text{-Bu}(\text{Me})_2\text{Si-}$ ,  $R_2 = \text{Phenyl}$ ,  $R_3 = \text{-CH=CH-Me}$ , and X and Y = Me and MeCO in Example 6;  $R_1 = t\text{-Bu}(\text{Me})_2\text{Si-}$ ,  $R_2 = \text{Phenyl}$ ,  $R_3 = \text{Benzyl}$ , and X and Y = Me and MeCO in Example 7;  $R_1 = t\text{-Bu}(\text{Me})_2\text{Si-}$ ,  $R_2 = \text{Phenyl}$ ,  $R_3 = \text{-CH=CH-Me}$ , and X and Y = Me and -COO(CH=CH-Me) in Example 10.

With respect to the Examiner's comments on the zinc compounds in paragraph (b) of claim 15, applicants submit that the claim language is sufficiently clear that they contemplate a mixture of zinc's with at least one of the copper compounds of paragraph (a). On page 8 of their specification, applicants have defined the specific copper compounds which can be employed. It is only the copper compounds of (a) which are in admixture with zinc in paragraph (b) of claim 15. Since the Examiner has not questioned whether the copper compounds of (a) work in the claimed process, one of ordinary skill would certainly not expect that a mixture of zinc with such copper compounds would not work. Applicants do not believe that their specification must contain an additional specific statement that the (b) group of catalysts will actually work. It is implied in the disclosure.

(9) Conclusion

For each of the foregoing reasons, applicants submit that the Final Rejection of claims 15-19 is improper and the decision of the Examiner should be reversed.

~~I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on~~

~~April 3, 2000~~

~~BURGESS RYAN AND WAYNE~~

~~By: [Signature]~~

~~Date: April 3, 2000~~

MJW/WRM/mg

Respectfully submitted,  
BURGESS, RYAN AND WAYNE

*[Signature]*

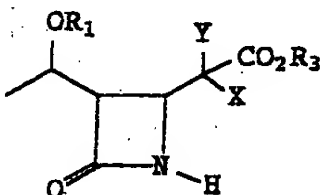
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# APPENDIX

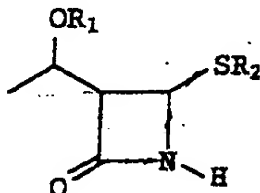
Pending Claims In Serial No. 09/178,594

15. A process for synthesizing a 4-substituted azetidinone derivative represented by the formula [3]:



[3]

which comprises reacting an azetidinone derivative represented by the formula [1]:



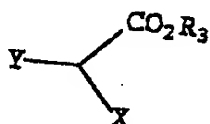
[1]

wherein OR<sub>1</sub> is a protected hydroxyl group; R<sub>2</sub> is a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkenyl group or a substituted or unsubstituted aromatic group, in the presence of:

(a) a copper compound selected from the group consisting of copper oxides, copper halides, salts of copper with

aliphatic and aromatic carboxylic acids, salts of copper with mineral acids and complexes of cuprous halides, or

(b) a mixture of zinc with at least one of said copper compounds with an ester compound represented by the formula [2]:



[2]

where  $\text{R}_3$  is a protective group easily removed therefrom;

wherein X and Y are the same or different and represent individually a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkenyl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted alkylthio group, a substituted or unsubstituted alkenylthio group, a substituted or unsubstituted aralkylthio group, a substituted or unsubstituted arylthio group, a substituted or unsubstituted alkyloxy group, a substituted or unsubstituted alkenyloxy group, a substituted or unsubstituted aralkyloxy group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted silyloxy group, a substituted or unsubstituted heterocyclic group, a substituted or unsubstituted heterocyclic-thio group, a substituted or unsubstituted heterocyclic-oxy group, a substituted or unsubstituted acyl group, a carboxyl group, an alkyloxycarbonyl



group, an alkenyloxycarbonyl group, an aralkyloxycarbonyl group, an aryloxycarbonyl group, a thiocarboxyl group, an alkylthiocarbonyl group, an alkenylthiocarbonyl group, an aralkylthiocarbonyl group, an arylthiocarbonyl group, a substituted or unsubstituted aminocarbonyl group, a substituted or unsubstituted amino group, a hydrogen atom or a halogen atom, or, when taken together with the carbon to which they are attached, form a substituted or unsubstituted cycloalkan-2-on-1-yl group;

wherein any substituents on  $R_2$  are selected from the group consisting of halogen, lower alkyl, monocyclic or polycyclic alkyl, lower alkoxy, carboxyl, amino, nitro, cyano, hydroxy, aryl of 6 to 10 carbon atoms and aralkyl groups of 7 to 24 carbon atoms;

wherein any substituents on X and Y are selected from the group consisting of halogen, carboxyl, formyl, nitro, cyano, hydroxyl, amino, lower alkyl, monocyclic and polycyclic alkyl, lower alkenyl, aryl of 6 to 10 carbon atoms, aralkyl of 7 to 24 carbon atoms, alkylthio, alkenythio, aralkythio, arylthio, alkyloxy, alkenyloxy, aralkyloxy, aryloxy, alkylsulfinyl, arylsulfonyl, carbamoyl, carbamoyloxy, imino-lower-alkyl, imino-lower-alkylamino, acyloxy, silyloxy, heterocyclic, heterocyclic-thio, heterocyclic-oxy, acyl, carboxyl, alkyloxycarbonyl, alkenyloxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl,

thiocarboxyl, alkylthiocarbonyl, alkenylthiocarbonyl, aralkylthiocarbonyl, arylthiocarbonyl and a substituted or unsubstituted aminocarbonyl group.

16. A process as claimed in claim 15 for synthesizing a 4-substituted azetidinone derivative represented by the formula [3], wherein said process further comprises the steps of treating an ester compound represented by the formula [2] with an alkali metal hydride to convert to the corresponding metal enolate, followed by reaction with an azetidinone derivative represented by the formula [1] in the presence of a copper compound.

17. A process as claimed in claim 15 wherein the ester compound represented by the formula [2] is a halogenated acetic acid ester, a malonic acid ester, a 2-alkylmalonic acid ester, a 2-halogenated malonic acid ester, a 2-alkyl-acylacetic acid ester or a cycloalkan-2-on-1-carboxylic acid ester.

18. A process as claimed in claim 15 wherein the ester compound represented by the formula [2] is a bromoacetic acid ester, a malonic acid ester, a 2-methylmalonic acid ester, a 2-fluoromalonic acid ester, a 2-methylacetoacetic acid ester or a cyclohexan-2-on-1-carboxylic acid ester.

19. A process as claimed in claim 15 wherein the copper compound is a cuprous bromide dimethylsulfide complex.

I believe that this case should go forward to the Board. There are the following issues:

1. The most important is a lack of Description of the catalyst. Claim 15, which is not an original claim, lists two catalysts in the alternative. Choice (a), which is a broad genus of copper compounds, is not a problem. Choice (b), the mixture of zinc with anything in (a) is beyond what the specification actually says. No such language appears in any form in the specification or original claims. The use of Zinc itself is described. There is also in Example 9 the use of Zinc with the cuprous bromide dimethyl sulfide complex. But single example of zinc with one particular Copper complex does not constitute a description of zinc with all of (a). Applicants have pointed to material at page 8, lines 4-18. But this material does not mention Zinc, and thus does not say that zinc can be mixed with anything in choice (a). That page 8 material simply describes what is in (a), which isn't the problem. The response in the Appeal Brief is largely in terms of enablement: "one of ordinary skill would certainly not expect that a mixture of zinc with such copper compounds would not work." However, as the examiner has repeatedly stated, the problem here is not a lack of enablement. The examiner does not question whether this would or would not work, only that the claim language is broader than the specification's language. The Appeal Brief says, "they contemplate a mixture of zinc's [sic, zinc] with at least one of the copper compounds of paragraph (a)." This is correct, but the claim language goes beyond that. Mixtures of Zinc with other than cuprous bromide dimethyl sulfide complex are simply never mentioned or embraced in any form, and there is no reason to think they were originally contemplated.
2. A second lack of description occurs in the definition of X and Y. Applicants have simply created choices which were never in the specification. For example, X and Y can be a carboxyl group, COOH; see Appendix, page 8, last line, middle term. The Appeal Brief, from the middle of page 4 to the bottom of page 5, points to page 2, lines 13+, to page 15-17 and to the working examples. Nowhere in there, however, is the COOH group mentioned as a choice for X and Y. The same is true for the thiocarboxyl, COSH, which is in the Appendix, page 9, line 2, second term. Applicants argue that, "one of ordinary skill would be aware that a wide variety of organic radicals could be present..." This is true; the specification does indeed set forth a wide variety of radicals, but that wide assortment does not include these choices. A second issue arises in this matter of the definition of X and Y. From Appendix, page 8, last line, last term through page 9, line 4 are a number of specific ester groups. These are defined much more specifically than appears in the specification. Page 2, line 13-14 does, as applicants point out, have "substituted or unsubstituted ester group, substituted or unsubstituted thioester group." These are very general terms, not specifying what type of acid (e.g. carboxylic or sulfonic), which end the group is bound via (e.g. -C(O)OR or -O(O)CR) or even what the nature of the R group is. And for the "thioester" it is ambiguous as to whether the S is in the double bonded position, e.g. -OC(S)R, or in the ester position, e.g. -SC(O)R. Applicants have created some very specific choices, such as alkenyloxycarbonyl, or aralkylthiocarbonyl. There are no guideposts to these specific choices, and hence these lack description.
3. The same problem occurs in the list of substituents attached to the various X and Y choices. That is X and Y can be e.g. substituted alkenylthio group, where there is a list of substituents set forth in the claim (see Appendix, page 9, starting at line 14). Thus, there is a carboxyl at the fifth from last line of claim 15, and a thiocarboxyl at the start of the third from last line of the claim. These terms never appear in the lengthy lists of substituents in

the specification. Similarly, the ester and thio ester choices which appear in the last 5 lines of claim 15 have the same problem as noted above. Applicants respond that "it may not be possible that each and every combination of X and/or Y with the substituent disclosed may exist chemically..." but that issue, an enablement question, was never raised. The examiner isn't saying that this substituent can't exist on that X and Y choice, but rather that applicants have created new choices for the list of substituents.

4. The amendment of July 13, 1999 broadened the definition of  $R_3$  so that it now reads "being a protective group easily removed therefrom". This is broader than the specification's language. Applicants point to Page 13, line 13 et seq. This says, "The group represented by  $R_3$  is not particularly limited, only if it can eliminate from the esterified carboxyl group through hydrolysis or under conditions of the selective procedure according to the type of esters...." Examples follow. This language is substantially garbled. The first part makes it clear that this is a group which can be hydrolyzed. The rest --- "or under conditions of the selective procedure according to the type of esters" --- is very vague. It appears that some sort of selectivity is required in the procedure. But the claim does not have such a limitation. It covers removable under any type of procedure, so long as it is easy to do. The specification doesn't really say that.

5. Further, the language of "easily removed" means that the claim is not to cover groups which can only be removed with difficulty. But where is the line between the two? The specification gives no guidance, because the term is nowhere present. Hence, the term is indefinite as well.

This case should clearly go to the Board of Patent Appeals and Interferences.



Mark Berch  
May 12, 2000